Conferences and Reviews

Glycemic Control and Complications of Diabetes Mellitus

Discussant
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This discussion was selected from the weekly Grand Rounds in the Department of Medicine, University of Washington School of Medicine, Seattle. Taken from a transcription, it has been edited by Dawn E. Dewitt, MD, Chief Medical Resident; Henry Rosen, MD, Professor and Associate Chair; and Paul G. Ramsey, MD, Professor and Chair of the Department of Medicine.

In an illustrative case, a 25-year-old man is seen for further evaluation of his diabetes mellitus. He was diagnosed with insulin-dependent (type I) diabetes mellitus (IDDM) after presenting with diabetic ketoacidosis at age 7. He has had no further hospital stays for his diabetes except for a recent vitrectomy and is currently managed with the daily administration of isophane insulin suspension (NPH) and regular insulin before breakfast. On physical examination, findings were notable for a blood pressure of 140/100 mm of mercury, multiple photocoagulation scars in both eyes, a sinus tachycardia at a rate of 100 beats per minute, poor vibratory sensation to the level of both knees, and trace peripheral edema. Laboratory evaluation reveals a hemoglobin A_{1c} (HbA_{1c}) fraction of 9.2% (normal, 4% to 6%), a serum albumin level of 33 grams per liter (3.3 mg per dl; normal, 35 to 50 grams per liter), and a serum creatinine level of 90 μmol per liter (1.0 mg per dl). Urine studies reveal 1.2 grams per 24 hours of protein with a creatinine clearance of 2.18 ml per second (130 ml per minute).

Background

The morbidity and mortality from IDDM are well appreciated.[1] In a widely quoted survey, 16% of patients with IDDM became blind, 31% died of uremia, and the median life span was 49 years.[2] The Joslin Diabetes Center (Boston, Massachusetts) published similar data, with 40% of patients diagnosed before the age of 20 years dying of uremia.[3] The cause of diabetic microvascular disease has been a subject of controversy. In the 1930s and 1940s, some physicians thought that hyperglycemia was an important predisposing factor. This "glucose hypothesis" was less favored because in some studies muscle basement membrane hypertrophy was thought to represent "an independent and, conceivably, even a primary lesion of the diabetic syndrome."[4] Experimental data from dogs and humans also suggest that insulin deficiency is somehow involved in the pathogenesis of microvascular disease.[5,6] Nevertheless, despite the controversy regarding the origin, there was a growing sentiment that treatment of the hyperglycemia could decrease the consequences of diabetic microangiopathy.[7]

In retrospect, several problems made these issues impossible to resolve. First, before the 1980s, glycemia could be estimated at home only with urine glucose measurements. The addition of occasional laboratory glucose measurements was not useful in a situation of frequent food and activity changes, illness, and emotional stresses. Furthermore, longer-acting insulins were developed 50 years ago to make the management of IDDM more convenient.[8] Many patients were administered one daily injection because this therapy could usually avoid ketosis and hypoglycemia, although patients seemed to do better on multiple administrations.[9] Indeed, the patient in the illustrative case presented here is a reminder of our earlier attempts at insulin therapy: success at preventing metabolic catastrophe, but not at preventing microvascular complications.

Since the discovery of insulin, perhaps the greatest development that improved the ability to manage patients with diabetes mellitus was the introduction of home blood glucose monitoring in the late 1970s and early 1980s. For the first time, patients could accurately measure blood glucose levels at home and make adjustments in their insulin dosage based on their level of glycemia, as opposed to the crude urine glucose testing of the past. Furthermore, researchers, clinicians, and patients for the first time could objectively quantitate overall glycemic control by the measurement of glycosylated hemoglobin fraction. The ability to use these new tools in an attempt to approximate normoglycemia with multiple injections and the newly developed insulin pump were greeted with enthusiasm by many, but not all. Nevertheless, the era of "intensive insulin therapy" was born in 1983 when all of the information to that date was assembled.[10]

In the early 1990s, this therapy was more widely accepted among endocrinologists[11,12] than among the primary care professionals who see most patients with

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ABBREVIATIONS USED IN TEXT

DCCT = Diabetes Control and Complications Trial
HbA_{1c} = hemoglobin A_{1c}
IDDM = insulin-dependent diabetes mellitus
NIDDM = non–insulin-dependent diabetes mellitus

diabetes in the United States.[13] A reason for this discrepancy was the lack of firm evidence that this newer therapy would be effective for preventing or retarding the complications of diabetes. There was also concern that maintaining normal blood glucose levels would result in the occurrence of frequent, dangerous, and unacceptable hypoglycemia.

Diabetes Control and Complications Trial

Rationale and Study Design

With the new ability to achieve normal or near-normal blood glucose levels, reports published in the 1980s tried to address the relationship between glycemic control and diabetic complications. Unfortunately, difficulties in experimental design complicated analysis of the studies. Many of the reports were retrospective, with prospective studies often nonrandomized and with relatively few study subjects. Furthermore, end points for characterizing the complications of diabetes mellitus often lacked precision. Nevertheless, by 1992 evidence was beginning to accumulate that poor glycemic control might be an important factor for the development and progression of diabetic complications.[14,15]

The Diabetes Control and Complications Trial (DCCT) was designed in 1982 and 1983 to ascertain whether intensive therapy for IDDM, directed at achieving blood glucose levels as close to the nondiabetic range as possible, would have a different effect on the incidence of diabetic complications than standard therapy. Given that it is not possible to prospectively assign a large number of patients different goals for glycemic control, the study was designed to test the differences in therapeutic programs, as opposed to differences in glycosylated hemoglobin levels.

The DCCT addressed two fundamental questions, the first relating to primary prevention. That is, in patients without any evidence of microvascular disease, could intensive therapy prevent its development? The second question concerned intervention. In patients with evidence of early microangiopathy, could intensive therapy prevent its progression? Retinopathy was the major end point because of its known epidemiology and relative ease in assessment. Therefore, persons in the primary-prevention cohort were required to have their IDDM for fewer than five years and to have no evidence of any diabetic retinopathy. Those in the secondary-intervention group were eligible if they had had their diabetes for less than 15 years and had minimal or moderate nonproliferative retinopathy. Early albuminuria (< 200 mg per day) was also allowed in this group, but was not required for study entry. By 1985, there were 29 centers in the United States and Canada participating, and they would eventually enroll a total of 1,441 subjects. All patients were between 13 and 39 years old when they were randomly assigned to intensive ("experimental") or conventional ("standard") therapy.

Conventional therapy was designed to mimic standard diabetes care in the community. These subjects administered insulin (intermediate and rapid-acting) once or twice a day, self-monitored urine or blood glucose levels daily (at the beginning of the study, only urine glucose testing was done), and received education about diet and exercise.[16] Subjects did not generally supplement insulin based on glucose monitoring. The primary clinical goals were to avoid the development of symptomatic hyperglycemia, frequent hypoglycemia, or ketonuria and to maintain normal growth, development, and ideal body weight. Women who became pregnant or were planning a pregnancy received intensive therapy until the time of delivery, after which they resumed conventional therapy. These subjects were seen in their clinics quarterly, and for this cohort, both patients and investigators were blinded to the women's hemoglobin A_{1c} levels.

Intensive therapy was designed to achieve normal blood glucose levels by administering at least three injections of insulin a day or by an insulin infusion pump. Subjects could switch back and forth from several injections to a pump if desired. Insulin doses were adjusted on a daily basis determined by a minimum of four daily home blood glucose measurements, dietary intake, and anticipated exercise. Glycemic goals included premeal glucose levels of between 3.9 and 6.67 mmol per liter (70 and 120 mg per dl), postprandial concentrations of less than 10.0 mmol per liter (180 mg per dl), and at least one weekly 3 AM measurement greater than 3.6 mmol per liter (65 mg per dl). The goal for the HbA_{1c} fraction was below 6.05%, as this was the upper limit of the normal range. Subjects had HbA_{1c} levels measured monthly at their clinic visits, and these were available for review by both the patients and the investigators. Subjects were often admitted to hospital to initiate intensive therapy and had frequent telephone contact between visits to review blood glucose records, if necessary.

Diagnosis of the primary end point, retinopathy, was based on seven-field stereoscopic fundus photographs taken every six months and assessed by graders unaware of the treatment-group assignments. The overall levels of severity of retinopathy were determined for each patient according to the Early Treatment Diabetic Retinopathy interim scale (Table 1).[17] Progression of the retinopathy was defined as a three-step change from baseline.

Other end points included nephropathy, neuropathy, and severe hypoglycemia. Nephropathy, which was assessed by annual timed urine collections for measuring urine albumin levels and creatinine clearance, supplemented by a more sensitive measure of the glomerular filtration rate, the iothalamate sodium I 125 clearance test. This test was initiated three years into and at the termination of the study. Microalbuminuria and clinical-grade albuminuria were defined as albumin excretion

TABLE 1.—*Retinopathy Grading Scale Used in the Diabetes Control and Complications Trial**

Step	Level of Retinopathy	Eligibility
1.....	No retinopathy	Primary prevention
2.....	Microaneurysms, one eye	Secondary intervention
3.....	Microaneurysms, both eyes	Secondary intervention
4-5.....	Mild NPDR	Secondary intervention
6-9.....	Moderate NPDR	Secondary intervention
10-13.....	Severe NPDR	
14-15.....	Mild PDR	
16-17.....	Moderate PDR	
18-25.....	High-risk PDR and worse	

NPDR = nonproliferative diabetic retinopathy, PDR = proliferative diabetic retinopathy

*From the Diabetes Control and Complications Trial Research Group.[19]

rates between 40 and 300 mg per 24 hours (27 and 201 μg per minute) or 300 mg per 24 hours and higher (201 μg per minute or higher), respectively. Neuropathy evaluations were based on a standard neurologic history and physical examination conducted by a specialist; nerve conduction studies in the median, peroneal, and sural nerves; and autonomic nervous system testing. Clinical neuropathy was defined as abnormal findings on physical examination consistent with the presence of peripheral sensorimotor neuropathy plus either abnormal nerve conduction in at least two peripheral nerves or abnormal autonomic nervous system responses to testing. Severe hypoglycemia was defined as an event with symptoms consistent with hypoglycemia in which the patient required the assistance of another person and that was associated with either a blood glucose level below 2.8 mmol per liter (50 mg per dl) or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration.[18]

Study Results

Glycemic Control

The entire study group of 1,441 subjects was observed for an average of 6.5 years (range, 3 to 9) for a total of 9,300 patient-years.[19] Significant differences in HbA_{1c} levels were maintained after baseline between the intensive-therapy and conventional-therapy groups in both cohorts ($P < .001$).[19] Less than 5% of patients in the intensive-therapy group maintained a normal glycosylated hemoglobin level throughout the study, while 44% of this group achieved this goal at least once. Quarterly seven-point capillary blood glucose profiles revealed mean (± standard deviation) values of 155 ± 30 mg per dl versus 231 ± 55 mg per dl for the intensive- and conventional-therapy groups, respectively ($P < .001$).

TABLE 2.—*Risk Reduction of Retinopathy With Intensive Therapy*

Outcome	Risk Reduction, %
Primary prevention	
≥1 Microaneurysm	27
≥3-Step progression	60
Sustained 3-step progression	76
Secondary intervention	
≥3-Step change	34
Sustained ≥3-step change	54
Proliferative or severe nonproliferative retinopathy	47
Laser treatment	56

Retinopathy

In the primary-prevention cohort, after five years' duration, the cumulative incidence of retinopathy in the intensive-therapy group was about 50% less than in the conventional-therapy group. The risk of the development of at least one microaneurysm was reduced by 27%, a single three-step progression by 60%, and sustained worsening of retinopathy by 76% in the primary prevention group (Table 2). Conclusions for more severe forms of retinopathy (proliferative and severe nonproliferative retinopathy or clinically important macular edema) could not be drawn because there were too few subjects in this group. In the secondary-intervention group, intensive therapy decreased a three-step progression by 54%, while reducing the incidence of proliferative or severe nonproliferative retinopathy and the need for laser therapy by 47% and 56%, respectively (Table 2). Patients in the intensive-therapy group had a higher cumulative incidence of sustained progression of retinopathy by three steps or more during the first year than did those in the conventional-therapy group, but a lower cumulative incidence beginning at 36 months and continuing for the rest of the study. As a secondary analysis, the relationship between the progression of retinopathy and HbA_{1c} levels was determined (Figure 1). This analysis showed a continuously increasing risk of sustained progression by three steps with increasing mean HbA_{1c} values.

Nephropathy

In both cohorts, microalbuminuria and clinical-grade albuminuria developed in fewer patients in the intensive-therapy group. Intensive therapy decreased the risk of microalbuminuria by 34% in the primary-prevention group and by 44% in the secondary-intervention cohort. The incidence of clinical-grade albuminuria was decreased by 43% (not significant) and 56% in the primary-prevention and secondary-intervention groups, respectively (Table 3).

Neuropathy

The treatment effect of intensive therapy was similar for neuropathy. Intensive therapy decreased the risk of clinical neuropathy for the primary-prevention and the secondary-intervention groups by 69% and 57%, respectively. The combined cohorts had a 60% risk reduction with intensive therapy. Individually, each component of the clinical neuropathy definition was reduced with

TABLE 3.—*Risk Reduction of Nephropathy With Intensive Therapy**

Outcome	Risk Reduction, %	P
Primary prevention		
UAE ≥40 mg/day (27 μg/min)	34	.04
UAE ≥300 mg/day (201 μg/min)	43	NS
Secondary intervention		
UAE ≥40 mg/day (27 μg/min)	44	.001
UAE ≥300 mg/day (201 μg/min)	56	.001
Both cohorts		
UAE ≥40 mg/day (27 μg/min)	39	≤.002
UAE ≥300 mg/day (201 μg/min)	54	<.04

NS = not significant, UAE = urinary albumin excretion

*Adapted from the Diabetes Control and Complications Trial Research Group.[19]

intensive therapy (examination, $P < .001$; autonomic nerve study, $P = .04$; nerve-conduction study, $P < .001$).

Macrovascular Disease

When combining all major cardiovascular and peripheral vascular events, intensive therapy reduced the risk by 41%, although this was not significant. Intensive therapy also reduced the development of hypercholesterolemia (defined as a low-density-lipoprotein-cholesterol level > 160 mg per dl) by 34%, but had no effect on the development of hypertriglyceridemia or hypertension.

Adverse Events and Safety

Mortality did not differ between the two treatment groups. In all, 11 subjects died, 7 of whom were in the intensive-therapy group. The event rates for diabetic ketoacidosis were similar in the two groups. The incidence of severe hypoglycemia was about three times higher in the intensive-therapy group than in the conventional-therapy group (Table 4). There were no deaths, myocardial infarctions, or strokes definitely attributable to hypoglycemia. Secondary analysis regarding the rate of severe hypoglycemia and increased HbA_{1c} fraction showed that the risk of severe hypoglycemia increased continuously with lower glycosylated hemoglobin values (Figure 1). Weight gain, another adverse event, was more prevalent with intensive therapy. At five years, patients receiving intensive therapy had gained a mean of 4.6 kg (10 lb) more than patients receiving conventional therapy. Finally, neuropsychological and quality-of-life testing did not show any differences between the two treatment groups. The added demands of intensive therapy in addition to the increased frequency of severe hypoglycemia in this group did not lead to any neurobehavioral changes.

Recommendations

It should again be noted that the DCCT was intended to ascertain if different forms of therapy for IDDM alter the natural history of diabetic complications. The data on

TABLE 4.—*Severe Hypoglycemia in the Diabetes Control and Complications Trial Combined Cohort*

Level of Hypoglycemia	Episodes/100 Patient-Years: Intensive Therapy	Episodes/100 Patient-Years: Conventional Therapy	Risk Ratio
Severe	62	19	3.3
Coma or seizure	16	5	3.0
ED or hospital admission	9	4	2.3
Deaths	0	0	--

ED = emergency department

glycemic goals for individual patients should be extrapolated with at least some caution because this was not the study design. Still, the results are conclusive and dramatic. Intensive therapy for IDDM resulting in a mean HbA_{1c} fraction of 7.2% compared with conventional therapy with a mean HbA_{1c} of 8.9% delays the development and slows the progression of diabetic retinopathy, nephropathy, and neuropathy by 35% to 70%. The major risk, however, severe hypoglycemia, was three times more common with intensive therapy. This is critical because DCCT study subjects had many more interactions with their health care teams than most patients with IDDM in the country.* In addition, this was a relatively homogeneous patient group, and thus conclusions generalized to all patients with diabetes mellitus need to be made with caution. Nevertheless, certain recommendations are now warranted.

The DCCT study group recommended that most patients with IDDM be treated with closely monitored intensive regimens with the goal of maintaining glycemia "as close to the normal range as safely possible."[19] This goal will need to be individually tailored because for many patients the risk-to-benefit ratio may not favor normoglycemia. The most obvious example are patients who are unaware they have hypoglycemia or who have a history of repeated episodes of severe hypoglycemia. An increasing number of patients seem to be attempting to achieve normal or near-normal levels of glycemia despite the risk of dangerous and occasionally life-threatening hypoglycemia. These patients need to be strongly encouraged to increase their glycemic targets. It is hoped that new strategies to combat this problem will be forthcoming.[20,21]

The DCCT study group also recommended that the data should not be extrapolated to apply to patients with advanced complications such as end-stage renal disease or cardiovascular or cerebrovascular disease.[19] Unfortunately, improved glycemic control does not appear to be effective in treating advanced retinopathy[22] or nephropathy.[23,24] Similarly, repetitive and severe hypoglycemia appears to be too risky for patients with substantial macrovascular disease. Improved control still may be protective for one type of complication

*See also the editorial by D. M. Nathan, MD, "Management of Diabetes Mellitus After the DCCT—What's Next?" on pages 469-470 of this issue.

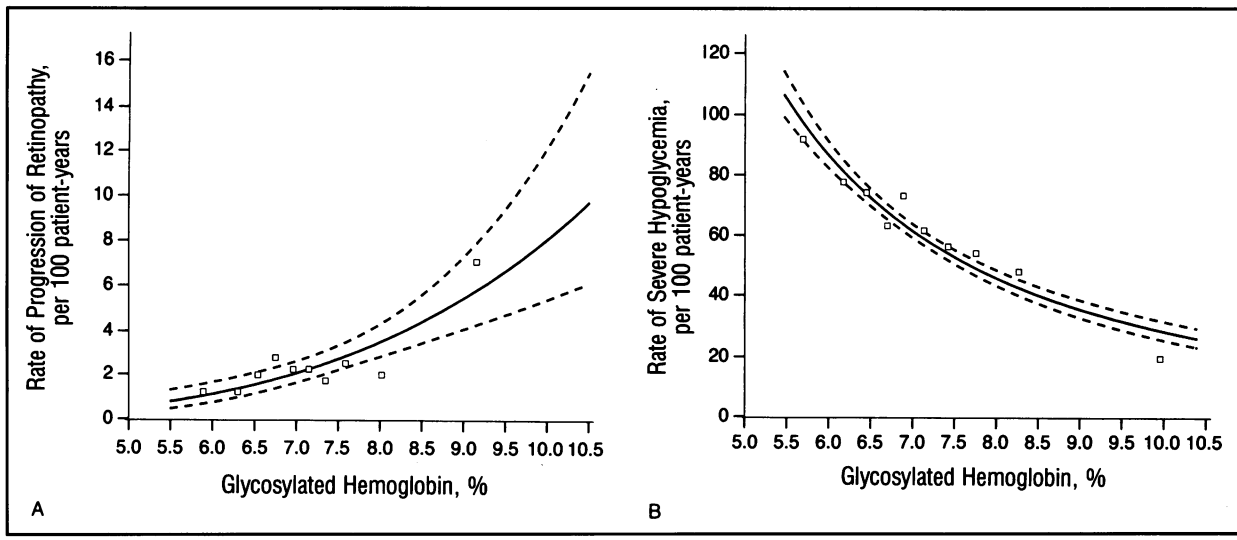

Figure 1.—**A**, The risk of sustained progression of retinopathy and (**B**) the rate of severe hypoglycemia in the patients receiving intensive therapy, according to their mean glycosylated hemoglobin values during the trial, are shown. A sustained change in the severity of retinopathy was defined as a change observed by fundus photography of at least 3 steps from baseline that was sustained for at least 6 months. In **A**, the glycosylated hemoglobin values used were the mean of the values obtained every 6 months. In **B**, the means of the monthly values were used. Open squares indicate the crude rates within deciles of the mean glycosylated hemoglobin values during the trial; each square corresponds to more than 400 patient-years. The lines are regression lines estimated as a function of the log of the mean glycosylated hemoglobin value in **A** and the log of the glycosylated hemoglobin value in **B**; the dashed lines are the 95% confidence intervals (reprinted with permission from *The New England Journal of Medicine*[19]).

after another one has developed, however. A variety of psychological benefits stem from improved glycemic control.[25,26]

Conclusions regarding the effects of intensive therapy should also be made with caution for children younger than 13 years.[19] Children below this age were not included in the study, and the evidence to date suggests that the contribution of the prepubertal years of diabetes mellitus to chronic complications may be minimal.[27]

Perhaps the greatest debate regarding the DCCT is how these data should be extrapolated to patients with non–insulin-dependent (type II) diabetes mellitus (NIDDM). Data to date certainly support an association of hyperglycemia with the presence or progression of complications in NIDDM.[28-31] Although it appears that the degree of hyperglycemia, not the type of diabetes, best predicts the development or progression of retinopathy and nephropathy, we are still awaiting the results of two prospective interventional studies in this patient population.[32,33] The DCCT study group and others have recommended caution in extrapolating the data to patients with NIDDM,[19,34,35] whereas the group at the National Institutes of Health has been less conservative.[36] There appears to be general agreement that for patients with NIDDM, it is most desirable that meticulous glycemic control be maintained through diet and exercise alone. Most patients will eventually require an oral hypoglycemic agent to maintain similar metabolic control. Preliminary data from the United Kingdom Prospective Diabetes study indicate that in 83% of patients with newly diagnosed NIDDM, treatment with diet alone fails within a year, and the patients require drug therapy.[37]

The controversy arises when exogenous insulin is required. After five years, only about half of patients who initially had excellent or good glycemic control with an oral agent still have a favorable response.[38] Evidence is accumulating that insulin may directly promote atherosclerosis.[39] Furthermore, it has been understood since the discovery of insulin that obese patients with NIDDM gain even more weight when started on insulin therapy.[9] Insulin administration for 3 to 12 months in these patients produces a mean weight gain of 6 kg (13 lb).[40] Certainly, improved glycemic control with the addition of a sulfonylurea may also cause weight gain.[37] In its position statement, the American Diabetes Association states that "there is no reason to believe that the effects of better control of blood glucose levels would not apply to people with NIDDM."[41(p1556)] It is also stressed that glycemic goals need to be tailored to each patient, especially older patients in whom severe hypoglycemia could have more devastating consequences (such as cardiovascular complications) than seen in the younger patients with IDDM studied in the DCCT.[41]

The DCCT results should also not be extrapolated to other forms of therapy that attempt to achieve normal blood glucose levels. For example, implantable insulin pumps, glucose sensors operating in conjunction with an internal or external insulin pump, and implanted microencapsulated islets will all have their own advantages and disadvantages.[42] Risk-to-benefit ratios with intensive therapy for IDDM should not be compared with those of the newer, as yet unproven, therapeutic strategies. Similarly, the DCCT results should not be interpreted as an endorsement for pancreas transplanta-

tion. Even though there have been some encouraging data regarding the beneficial effects of pancreas transplantation on neuropathy and nephropathy (but not retinopathy),[43,44] this form of therapy requires lifelong immunosuppression and cannot be recommended as a routine treatment modality.[45]

Implications

Medical Implications

The DCCT was not designed to study the effects of different levels of glycosylated hemoglobin on microvascular complications. The DCCT investigators realized it would not be possible to prospectively assign patients to different glycemic goals. Rather, the trial was undertaken to study the effects of two different treatment regimens (intention-to-treat study). Nevertheless, the secondary analyses comparing the progression of retinopathy and severe hypoglycemia with the levels of HbA_{1c} were impressive.

Another issue the DCCT addressed is the possibility that there is a threshold level of hyperglycemia where the progression of retinopathy appeared. In the secondary analysis, it was shown that at each increased level of HbA_{1c}, the progression of retinopathy increased in a curvilinear relationship (Figure 1). Stated differently, any sustained decrease of HbA_{1c} will decrease the risk of retinopathy to progress. This is encouraging because less than 5% of the subjects in the DCCT maintained their HbA_{1c} levels within the normal range. Although levels of glycemic control established in the DCCT may be difficult to achieve, there are still benefits even if blood glucose levels are not "normalized." The secondary analyses for albuminuria and neuropathy are not yet available, but will be reported in the future.

The DCCT confirmed the results of other trials revealing a transient worsening of retinopathy with intensive therapy.[46,47] These retinal changes consisted of the development of soft exudates or intraretinal microvascular abnormalities in 22% of the intensive-therapy group compared with 13% of the conventional-therapy group of the secondary-intervention cohort during the first year. Because the abnormalities generally disappeared by 18 months, the DCCT study group recommends that the worsening of retinopathy should not deter clinicians from using intensive therapy.[19] Subjects with early worsening had a 74% reduction in the risk of subsequent progression compared with patients with early worsening who received conventional therapy. It should be pointed out that the DCCT did not study patients who at randomization had severe nonproliferative retinopathy or mild proliferative retinopathy. Conclusions about transient worsening of retinopathy in these patients are not possible, and physicians will have to proceed with caution with this group.

Another adverse effect of intensive therapy, weight gain, was an early observation from the DCCT.[48] Several studies have shown that patients with IDDM will gain about 5 kg (11 lb) during the first year of intensive therapy.[48-50] It has recently been shown that 70% of weight gain with intensive therapy could be accounted for by the elimination of glycosuria and 30% by the reduction of energy expenditure.[51] Follow-up of the DCCT patients over the next decade will help determine the effects of this extra weight, especially with regard to cardiovascular disease. It is hoped that the benefit of intensive therapy will outweigh the adverse effects of weight gain by reducing the incidence of diabetic nephropathy, the major risk for early death in patients with IDDM.[2] Neither the clinical importance of this weight gain nor its mechanism should be extrapolated to patients with NIDDM.

The most worrisome medical implication of the results of the DCCT is the increased risk of hypoglycemia. Previous estimates suggest that patients with IDDM may have 2,000 to 4,000 symptomatic episodes of hypoglycemia over a 40-year span.[52] Furthermore, approximately 4% of patients with IDDM die of hypoglycemia.[52] Because these data are based on conventional therapies of the past, how will the epidemiology of this event, with its associated morbidity and mortality, change with intensive therapy? In the DCCT, a threefold increase in the incidence of severe hypoglycemia occurred with the imperfect (yet improved) insulin replacement regimens of multiple administrations and insulin pumps. This increase occurred despite the frequent patient interactions with an expert team of diabetologists, nurses, nutritionists, and behavioral specialists who sought to minimize the frequency of hypoglycemia. How common will severe hypoglycemia be in the context of intensive therapy in a conventional venue, be it a physician's office, a university-based clinic, or a health maintenance organization? Both the DCCT Research Group and the American Diabetes Association caution that intensive therapy may not be appropriate for all patients, especially those who are unaware when they have hypoglycemia.[19,41] Patients who are unable or unwilling to monitor blood glucose levels regularly should not be encouraged to achieve normal blood glucose concentrations. Nevertheless, the devastating microvascular complications that appear to be due to hyperglycemia[36] lead to a risk-to-benefit ratio that favors intensive therapy for most patients with IDDM.[19,34-36,41]

The other immediate medical problem that both practitioners and patients need to understand is the lack of standardization of glycosylated hemoglobin assays. In the DCCT, HbA_{1c} levels were measured by a central laboratory with a nondiabetic range of 5.05% ± 0.5%. Unfortunately, a variety of methods (and normal ranges) are used for measuring glycosylated hemoglobin, and thus physicians should not directly extrapolate DCCT HbA_{1c} concentrations as targets for their patients. Although it is now possible for clinical laboratories to standardize this important measurement,[53] few do so.

Social Implications

The overall cost of diabetes mellitus in 1992 was $91.8 billion, of which half was due to direct costs.[54]

Much of this cost is for the care of the complications. Direct inpatient care costs for chronic complications were $9.7 billion.[54] The total cost of diabetes has more than quadrupled since 1987.[54] Intensive therapy is about two to three times more expensive than conventional therapy, primarily due to supplies. Blood glucose strips alone, at about $0.50 each, are too expensive for many patients. Over a one-year period, glucose strips could cost $730 for patients who practice intensive therapy and measure their blood glucose concentrations four times a day. Being monitored by diabetes clinical nurse specialists and nutritionists would be an added expense for many. Although the results of the DCCT are dramatic, is implementation affordable in our struggle for reducing the costs of health care? A cost-benefit analysis should be released in the near future to address this question. It may be that intensive therapy for IDDM will be an excellent investment because of the financial savings of preventing or retarding the development of complications.

While we are awaiting the cost-benefit analysis, how are we to afford this therapy, given the constraints of managed care? For primary care physicians on a capitated budget, managed care has been described as a "powerful disincentive to quality care for patients with diabetes."[55] One of our major challenges should be to determine how we can treat diabetes at an intensity to yield outcomes similar to those shown in the DCCT but in the most cost-efficient manner possible. Further studies for many chronic diseases are clearly needed in this area.

Another important issue that requires review concerns the effects of the general attitudes and practice behaviors of primary care physicians who treat patients with IDDM. Primary care physicians' attitudes may help patients achieve good glycemic control.[56-58] Attitudes are not enough, however. Physicians also need a basic understanding of how to achieve maximal glycemic control. Unfortunately, a recent survey concluded that "primary care physicians are not fully aware of recommended criteria for intensive treatment of blood glucose in IDDM."[13(p765)] In this survey of general practitioners, family physicians, and internists, fewer than half of respondents thought that achieving the target glycosylated hemoglobin fraction was important, 38% routinely used a dietitian and nurse educator, and only 50% recommended two or more daily injections to manage IDDM.[13] Other recent reports have shown similar major deficiencies in the practice behaviors of primary care physicians.[59-62] The importance of these data cannot be overemphasized because in a recent survey, 96% of outpatient visits for primary care by patients with diabetes were made to general and family practitioners and internists.[63] Our fundamental challenge, therefore, is to provide intensive therapy for the large number of people in this country with IDDM who could benefit from it. Unfortunately, most physicians lack the training to provide this therapy. Because many of these primary care physicians—general internists, family physicians, general pediatricians—each has only a few patients with IDDM who would require intensive therapy (at least as carried out in the DCCT), it would not be cost- or time-efficient to provide this intensity of service.[36] A typical primary care practice is likely to have fewer than ten patients with IDDM.[64,65] Therefore, ideally many of these patients should be referred to centers with the expertise for this level of therapy, providing there is adequate collaboration with the referring physician.[36,66] At the very least, there needs to be a greater emphasis on continuing medical education about diabetes-related topics for primary care physicians[13,67] and physicians in training. The controversy of who is best suited to care for patients with diabetes mellitus is not new,[68] but as fewer young physicians are choosing endocrinology as a career,[69] family physicians, general internists, and pediatricians will have a greater role in providing primary care for these patients.

Several models of diabetes care have recently been developed that try to address these problems. In one model, which would be more appropriate for patients with IDDM, the "diabetes intensive management team" would provide all primary care.[70] Although this team would usually include a diabetologist, any physician could lead this team as long as he or she had developed the appropriate skills. With this model, it also may be appropriate to have a different provider manage non–diabetes-related problems. For patients with NIDDM, the model could be altered so that the diabetes team is used as often as deemed necessary by the primary care provider. For these models to be effective, communication must be adequate so that care can be integrated.[70]

Another evolving model for diabetes management in a primary care setting is "staged diabetes management."[64,71] In this setting, practice guidelines are developed for a particular community and clinical pathways (decision paths) are developed both for IDDM and NIDDM. In addition, detailed narratives and flowcharts allow a primary care provider to initiate, adjust, and maintain treatment. Specific criteria have been developed for referral to an endocrinologist. Initial results of staged diabetes management are encouraging,[71] and further research will be welcomed.

Finally, few patients and their physicians have the support of nurses, dietitians, and behavioral scientists such as were available to the DCCT patients. Unfortunately, the concept of the "diabetes team" is poorly understood.[67] Acknowledging that the center of any team is the patient, we should better use other team members as "physician extenders."[72] In the DCCT, most of the patient interaction was not with the physician, but with these other team members. Placing the emphasis of diabetes care with these other highly qualified personnel, with a physician supervising, is also more cost-efficient. This treatment strategy was dramatically successful in reducing the incidence and progression of microvascular complications in the DCCT. It is now time to implement this therapy for all appropriate patients.

Acknowledgment

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REFERENCES

1. Nathan DM: Long-term complications of diabetes mellitus. N Engl J Med 1993; 328:1676-1685

2. Deckert T, Poulsen JE, Larsen M: Prognosis of diabetics with diabetes onset before the age of thirty-one—I: Survival, causes of death, and complications. Diabetologia 1978; 14:363-370

3. Marks HH, Krall LP: Onset, course, prognosis, and mortality in diabetes mellitus, chap 9. *In* Marble A, White P, Bradley RF, Krall L (Eds): Joslin's Diabetes Mellitus, 11th edition. Philadelphia, Pa, Lea & Febiger, 1971, pp 209-254

4. Siperstein MD: Capillary basement membranes and diabetic microangiopathy. Adv Intern Med 1972; 18:325-344

5. Engerman R, Bloodworth JMB Jr, Nelson S: Relationship of microvascular disease in diabetes to metabolic control. Diabetes 1977; 26:760-769

6. Feingold DR, Lee TH, Chung MY, Siperstein MD: Muscle capillary basement membrane width in patients with vacor-induced diabetes mellitus. J Clin Invest 1986; 78:102-107

7. Tattersall RB: The quest for normoglycaemia: A historical perspective. Diabet Med 1994; 11:618-635

8. Bliss M: The history of insulin. Diabetes Care 1993; 16(suppl 3):4-7

9. Sönksen PH: The evolution of insulin treatment. Clin Endocrinol Metab 1977; 6:481-497

10. Schade DS, Santiago JV, Skyler JS, Rizza R: Intensive Insulin Therapy. Princeton, NJ, Excerpta Medica, 1983

11. Hirsch IB, Farkas-Hirsch R, Skyler JS: Intensive insulin therapy for the treatment of type I diabetes. Diabetes Care 1990; 13:1265-1283

12. Santiago JV: Insulin therapy in the last decade: A pediatric perspective. Diabetes Care 1993; 16(suppl 3):143-154

13. Tuttleman M, Lipsett L, Harris MI: Attitudes and behaviors of primary care physicians regarding tight control of blood glucose in IDDM patients. Diabetes Care 1993; 16:765-772

14. Strowig S, Raskin P: Glycemic control and diabetic complications. Diabetes Care 1992; 15:1126-1140

15. Santiago JV: Intensive management of insulin dependent diabetes: Risks, benefits and unanswered questions. J Clin Endocrinol Metab 1992; 75:977-982

16. DCCT Research Group: The Diabetes Control and Complications Trial (DCCT): Design and methodologic considerations for the feasibility phase. Diabetes 1986; 35:530-545

17. Early Treatment Diabetic Retinopathy Study Research Group: Grading diabetic retinopathy from stereoscopic color fundus photographs—An extension of the modified Airlic House classification: ETDRS report No. 10. Ophthalmology 1991; 98:786-806

18. DCCT Research Group: Epidemiology of severe hypoglycemia in the Diabetes Control and Complications Trial. Am J Med 1991; 90:450-459

19. Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329:977-986

20. Cryer PE: Hypoglycemia begets hypoglycemia in IDDM. Diabetes 1993; 42:1691-1693

21. Maran A, Cranston I, Lomas J, Macdonald I, Amiel SA: Protection by lactate of cerebral function during hypoglycemia. Lancet 1994; 343:16-20

22. Ramsay RC, Goetz FC, Sutherland DER, et al: Progression of diabetic retinopathy after pancreas transplantation for insulin-dependent diabetes mellitus. N Engl J Med 1988; 318:208-214

23. Viberti GC, Bilous RW, Mackintosh D, Bending JJ, Keen H: Long-term correction of hyperglycaemia and progression of renal failure in insulin-dependent diabetes. Br Med J [Clin Res] 1983; 286:598-602

24. Fioretto P, Mauer SM, Bilous RW, Goetz FC, Sutherland DER, Steffes MW: Effects of pancreas transplantation on glomerular structure in insulin-dependent diabetic patients with their own kidneys. Lancet 1993; 342:1193-1196

25. Houtzagers CMGJ, Visser AP, Berntzen PA, et al: Multiple daily insulin injections improve self-confidence. Diabet Med 1989; 6:512-519

26. Seigler DE, LaGreca AM, Citrin WS, Reeves ML, Skyler JS: Psychological effects of intensification of diabetic control. Diabetes Care 1982; 5(suppl 1):19-23

27. Kostraba JN, Dorman JS, Orchard TJ, et al: Contribution of diabetes duration before puberty to development of microvascular complications in IDDM subjects. Diabetes Care 1989; 12:686-693

28. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL: The Wisconsin epidemiologic study of diabetic retinopathy—III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. Arch Ophthalmol 1984; 102:527-532

29. Nathan DM, Singer DE, Godine JE, Harrington CH, Perlmutter LC: Retinopathy in older type II diabetics: Association with glucose control. Diabetes 1986; 35:797-801

30. Green DA, Sima AAF, Stevens MJ, Feldman EL, Lattimer SA: Complications: Neuropathy, pathogenic considerations. Diabetes Care 1992; 15:1902-1925

31. Klein R, Klein BEK, Moss SE: Incidence of gross proteinuria in older-onset diabetes: A population-based perspective. Diabetes 1993; 42:381-389

32. UK Prospective Diabetes Study Group: UK Prospective Diabetes Study (UKPDS)—VIII. Study design, progress and performance. Diabetologia 1991; 34:877-890

33. Abraira C, Emanuele N, Colwell J, et al, and the VA Cooperative Study Group (CSDM): Glycemic control and complications in type II diabetes: Design of a feasibility trial. Diabetes Care 1992; 15:1560-1571

34. Lasker RD: The Diabetes Control and Complications Trial: Implications for policy and practice (Editorial). N Engl J Med 1993; 329:1035-1036

35. Palumbo PJ: Diabetes Control and Complications Trial: The continuing challenge ahead (Editorial). Mayo Clin Proc 1993; 68:1126-1127

36. Eastman RC, Siebert CW, Harris M, Gorden P: Implications of the Diabetes Control and Complications Trial. J Clin Endocrinol Metab 1993; 77:1105-1107

37. Multicentre Study: UK prospective study of therapies of maturity-onset diabetes—I. Effect of diet, sulphonylurea, insulin, or biguanide therapy on fasting plasma glucose and body weight over one year. Diabetologia 1983; 24:404-411

38. Lebovitz HE: Sulfonylurea drugs, chap 18. *In* Lebovitz HE (Ed): Therapy for Diabetes Mellitus and Related Disorders. Alexandria, Va, American Diabetes Association, 1994, pp 116-123

39. Stout RW: Insulin and atheroma: 20-yr perspective. Diabetes Care 1990; 13:631-654

40. Genuth S: Insulin use in NIDDM. Diabetes Care 1990; 13:1240-1264

41. American Diabetes Association (Position Statement): Implications of the Diabetes Control and Complications Trial. Diabetes 1993; 42:1555-1558

42. Saudek CD: Future developments in insulin delivery systems. Diabetes Care 1993; 16(suppl 3):122-132

43. Robertson RP: Pancreatic and islet transplantation for diabetes—Cures or curiosities? N Engl J Med 1992; 327:1861-1868

44. American Diabetes Association: Pancreas transplantation for patients with diabetes mellitus (technical review). Diabetes Care 1992; 15:1668-1672

45. American Diabetes Association: Pancreas transplantation for patients with diabetes mellitus (position statement). Diabetes Care 1992; 15:1673

46. Kroc Collaborative Study Group: Blood glucose control and the evolution of diabetic retinopathy and albuminuria: A preliminary multicenter trial. N Engl J Med 1984; 311:365-372

47. Dahl-Jørgensen K, Brinchmann-Hansen O, Hanssen KF, Sandvik L, Aagenaes O: Rapid tightening of blood glucose control leads to transient deterioration of retinopathy in insulin-dependent diabetes mellitus: The Oslo study. Br Med J [Clin Res] 1985; 290:811-815

48. DCCT Research Group: Weight gain associated with intensive therapy in the Diabetes Control and Complications Trial. Diabetes Care 1988; 11:567-573

49. Wing RR, Klein R, Moss SE: Weight gain associated with improved glycemic control in population-based sample of subjects with type I diabetes. Diabetes Care 1990; 13:1106-1109

50. Leslie P, Jung RT, Isles TE, Baty J, Newton RW, Illingworth P: Effect of optimal glycaemic control with continuous subcutaneous insulin infusion on energy expenditure in type I diabetes mellitus. Br Med J [Clin Res] 1986; 293:1121-1126

51. Carlson MG, Campbell PJ: Intensive insulin therapy and weight gain in IDDM. Diabetes 1993; 42:1700-1707

52. Cryer PE, Binder C, Bolli GB, et al: Hypoglycemia in IDDM. Diabetes 1989; 38:1193-1199

53. Bodor GS, Little RR, Garrett N, Brown W, Goldstein DE, Nahm MJ: Standardization of glycohemoglobin determinations in the clinical laboratory: Three years of experience. Clin Chem 1992; 38:2414-2418

54. Direct and Indirect Costs of Diabetes in the United States in 1992. Alexandria, Va, American Diabetes Association, 1993

55. Herter CD: Primary-care physicians, HMO's and the DCCT. Clin Diabetes 1993; 11:98-99

56. Weinberger M, Cohen SJ, Mazuca SA: The role of physicians' knowledge and attitudes in effective diabetes management. Soc Sci Med 1984; 19:965-969

57. Pringle M, Stewart-Evans C, Coupland C, Williams I, Allison S, Sterland J: Influences on control in diabetes mellitus: Patient, doctor, practice or delivery of care? BMJ 1993; 306:630-634

58. Kinmonth AL, Marteau TM: Doctors' beliefs and the management of insulin-dependent diabetes: Implications for shared care. Fam Pract 1989; 6:193-198

59. Kenny SJ, Smith PJ, Goldschmid MG, Newman JM, Herman WH: Survey of physician practice behaviors related to diabetes mellitus in the U.S. Diabetes Care 1993; 16:1507-1510

60. Miller KL, Hirsch IB: Physicians' practices in screening for the development of diabetic nephropathy and the use of glycosylated hemoglobin levels. Diabetes Care 1994; 17:1495-1497

61. Jacques CHM, Jones RL, Houts P, et al: Reported practice behaviors for medical care of patients with diabetes mellitus by primary care physicians in Pennsylvania. Diabetes Care 1991; 14:712-717

62. Marrero DG, Moore PS, Fineberg NS, Langefeld CD, Clark CM Jr: The treatment of patients with insulin-requiring diabetes mellitus by primary care physicians. J Community Health 1991; 16:259-267

63. Harris MI: Testing for blood glucose by office-based physicians in the US. Diabetes Care 1990; 13:419-426

64. Mazze R, Etzwiler D, Strock E, et al: Staged diabetes management: Toward an integrated model of diabetes care. Diabetes Care 1994; 17(suppl 1):56-66

65. Peterson K, McClure CR, Mezzaros J, et al: Diabetes care by primary care physicians in Minnesota and Wisconsin. J Fam Pract 1994; 38:361-368

66. Santiago JV: Lessons from the Diabetes Control and Complications Trial. Diabetes 1993; 42:1549-1554

67. Farkas-Hirsch R, Hirsch IB: A time for a change. Diabetes Care 1993; 16:660-661

68. Home P, Walford S: Diabetes care: Whose responsibility? Br Med J [Clin Res] 1984; 289:713-714

69. Petersdorf RG, Goitein L: The future of internal medicine. Ann Intern Med 1993; 119:1130-1137

70. Eastman RC, Gorden P: The DCCT: Implications for diabetes management. Diabetes Rev 1994; 2:263-271

71. Mazze RS, Etzwiler DD: Implications of the DCCT for national health care reform: Specialty versus primary physician care for type I diabetes—Point. Diabetes Rev 1994; 2:256-262

72. Farkas-Hirsch R, Hirsch IB: Role of diabetes educator in patient management, chap 12, *In* Lebovitz HE (Ed): Therapy for Diabetes Mellitus and Related Disorders. Alexandria, Va, American Diabetes Association, 1994, pp 83-86